

methoxy erythromycin respectively by fermentation with an appropriate *eryA* mutant that is incapable of producing 6-dEB and in which the *eryF* (C-6 hydroxylase) function has been deleted or otherwise inactivated. Fermentation of 6-OH or 6-OMe aglycone with an *eryA* mutant that possesses *eryF* (or equivalent) function leads to the 6-desmethyl-6-oxo erythromycin.

On page 27, at line 20 thereof, after "Two", please replace "embodiment" with --embodiments--, as indicated below for the paragraph beginning at line 18:

In another aspect of the present invention, methods for converting the 3'-desmethyl erythromycin oximinoester into 3'-desmethyl-R erythromycin oximinoesters are provided. Two [embodiment] embodiments are illustrated in Scheme 8.

Amendments to the Claims

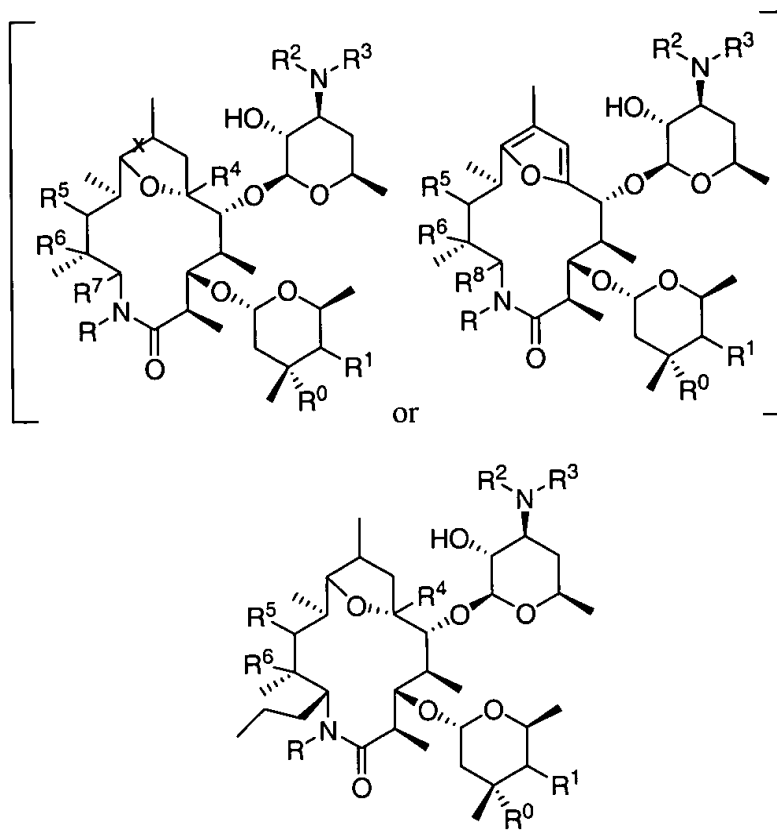
Please amend the claims as follows. A set of claims reflecting the amendments below is included herewith.

✓ Please cancel claims 3-6 and 12-17 without prejudice to further prosecution in a related application, including without limitation: a divisional, continuation, or continuation-in-part application.

Please amend claims 1, 2, 7-11, 18, and 19 as follows.

Serial No. 09/990,554
Attorney Docket No. 010041.02

1. (Amended) A compound of the formula



wherein:

R is hydrogen, substituted C₁-C₁₀ alkyl, unsubstituted C₁-C₁₀ alkyl, substituted C₂-C₁₀ alkenyl, unsubstituted C₂-C₁₀ alkenyl, substituted C₂-C₁₀ alkynyl, unsubstituted C₂-C₁₀ alkynyl, substituted aryl, unsubstituted aryl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl;

R⁰ is hydroxyl or methoxy;

R¹ is selected from the group consisting of hydrogen, hydroxyl, halide, NH₂, OR⁹, OCR^9 , $\text{OCNR}^{10}\text{R}^{11}$, NCR^9 , $\text{CNCR}^{10}\text{R}^{11}$ where R⁹ is substituted C₁-C₁₀ alkyl, unsubstituted C₁-C₁₀ alkyl, substituted C₂-C₁₀ alkenyl, unsubstituted C₂-C₁₀ alkenyl, substituted C₂-C₁₀ alkynyl, unsubstituted C₂-C₁₀ alkynyl, substituted aryl, unsubstituted

aryl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl, and R^{10} and R^{11} are each independently hydrogen, substituted C_1 - C_{10} alkyl, unsubstituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, unsubstituted C_2 - C_{10} alkynyl, substituted aryl, unsubstituted aryl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, substituted C_1 - C_{10} alkyl, unsubstituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, unsubstituted C_2 - C_{10} alkynyl, substituted aryl, unsubstituted aryl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, and unsubstituted alkynylaryl, or R^2 and R^3 together form a cycloalkyl or an aryl moiety;

R^4 is hydrogen or methyl;

R^5 is hydroxyl or oxo;

R^6 is hydrogen, hydroxyl, or OR^{12} where R^{12} is substituted C_1 - C_{10} alkyl, unsubstituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, or unsubstituted C_2 - C_{10} alkynyl; and

[R^7 is methyl, unsubstituted C_3 - C_{10} alkyl, substituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, unsubstituted C_2 - C_{10} alkynyl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, and unsubstituted alkynylaryl];

R^8 is unsubstituted C_1 - C_{10} alkyl, substituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, unsubstituted C_2 - C_{10} alkynyl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl]; and,

x is a single or a double bond].

2. (Amended) The compound as in claim 1 wherein

R is hydrogen, methyl, ethyl, propyl, isopropyl, phenyl or benzyl; R⁰ is hydroxyl or methoxy;

R¹ is hydrogen or hydroxyl;

R² is methyl;

R³ is methyl, ethyl, propyl, isopropyl, butyl, isobutyl, secbutyl, or tertbutyl;

R⁴ is methyl;

R⁵ is hydroxyl;

R⁶ is hydroxyl or methoxy; and

[R⁷ is methyl, vinyl, propyl, isobutyl, pentyl, prop-2-enyl, propargyl, but-3-enyl, 2-azidoethyl, 2-fluoroethyl, 2-chloroethyl, cyclohexyl, phenyl, or benzyl;]

R⁸ is methyl, ethyl, vinyl, propyl, isobutyl, pentyl, prop-2-enyl, propargyl, but-3-enyl, 2-azidoethyl, 2-fluoroethyl, 2-chloroethyl, cyclohexyl, phenyl, or benzyl; and,

x is single bond or a double bond].

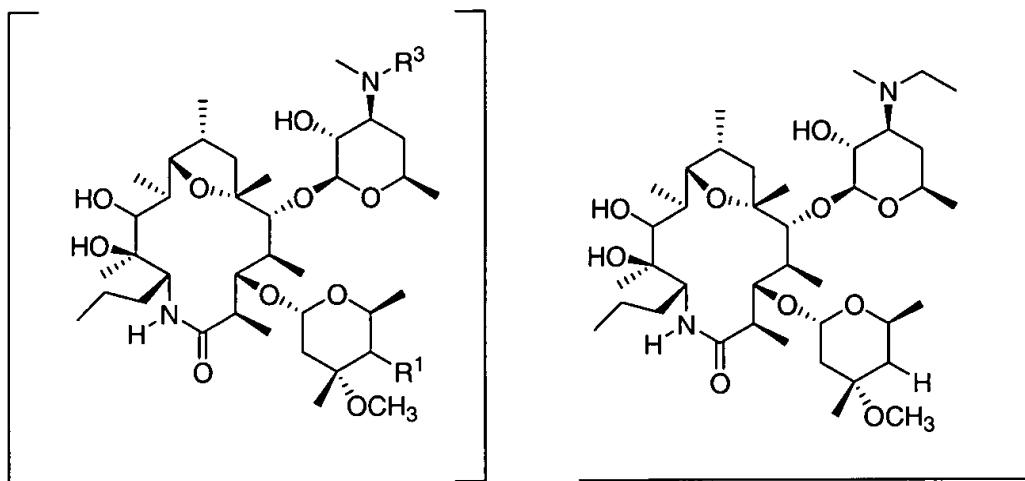
7. (Amended) The compound as in Claim [6] 1 wherein

R³ is methyl, ethyl, or isopropyl;

[R⁷ is propyl or fluoroethyl;] and

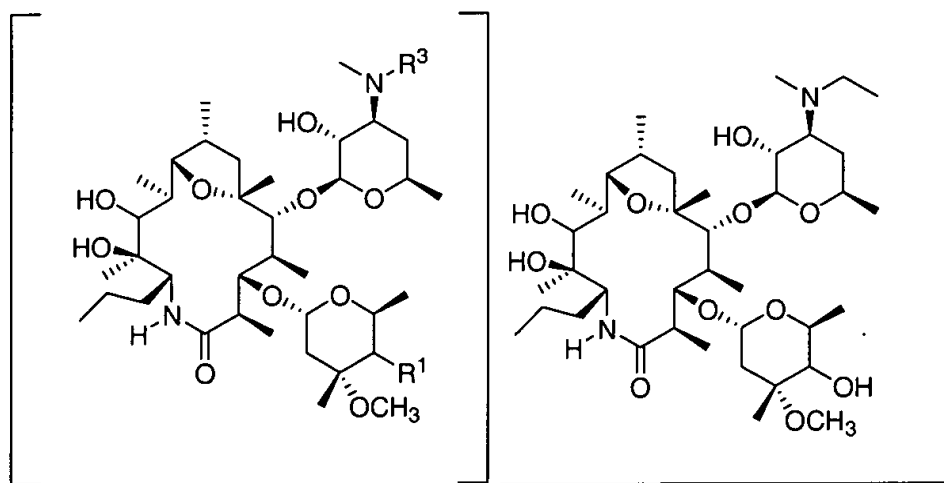
R⁸ is ethyl, propyl, or 2-fluoroethyl.

8. (Amended) The compound as in claim 7 of the formula



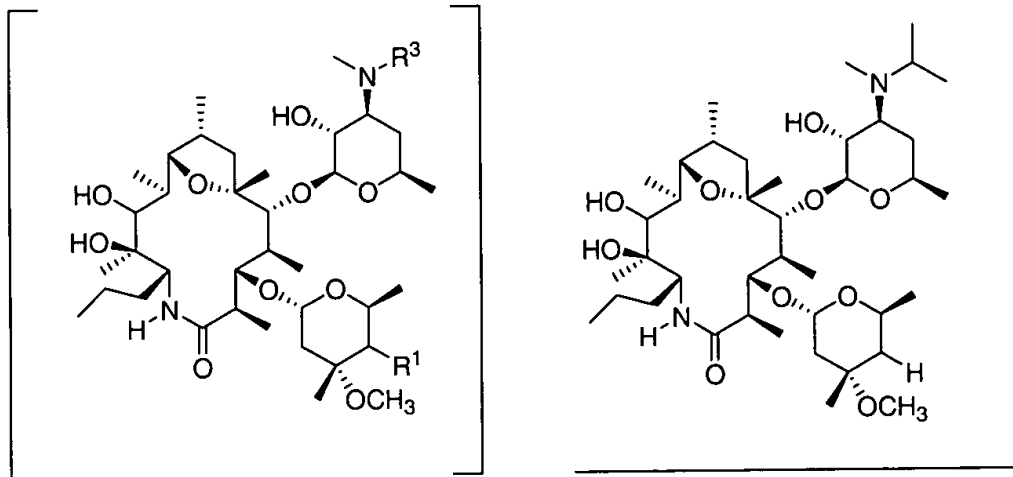
[wherein R^1 is hydrogen, R^3 is ethyl and R^7 is propyl].

9. (Amended) The compound as in Claim 7 of the formula



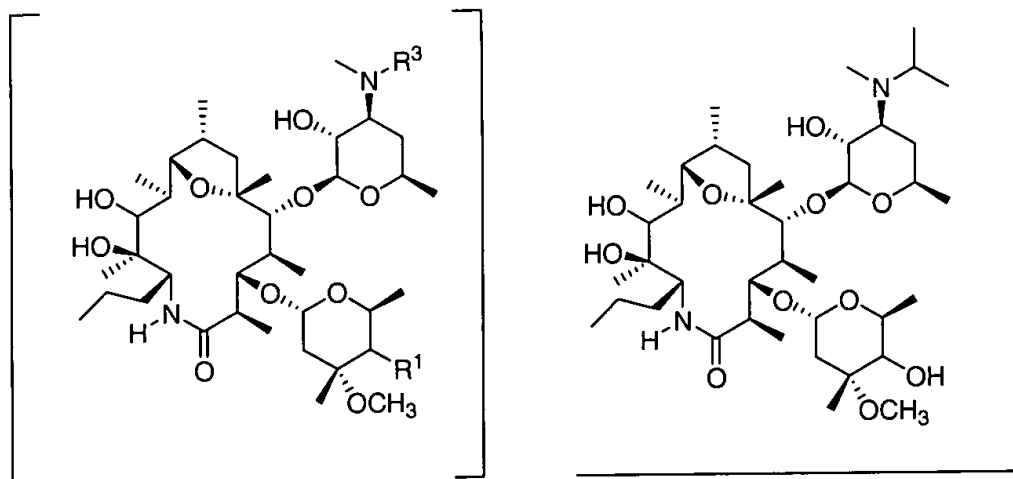
[wherein R^1 is hydroxyl, R^3 is ethyl and R^7 is propyl].

10. (Amended) The compound as in claim 7 of the formula



[wherein R¹ is hydrogen, R³ is isopropyl and R⁷ is propyl].

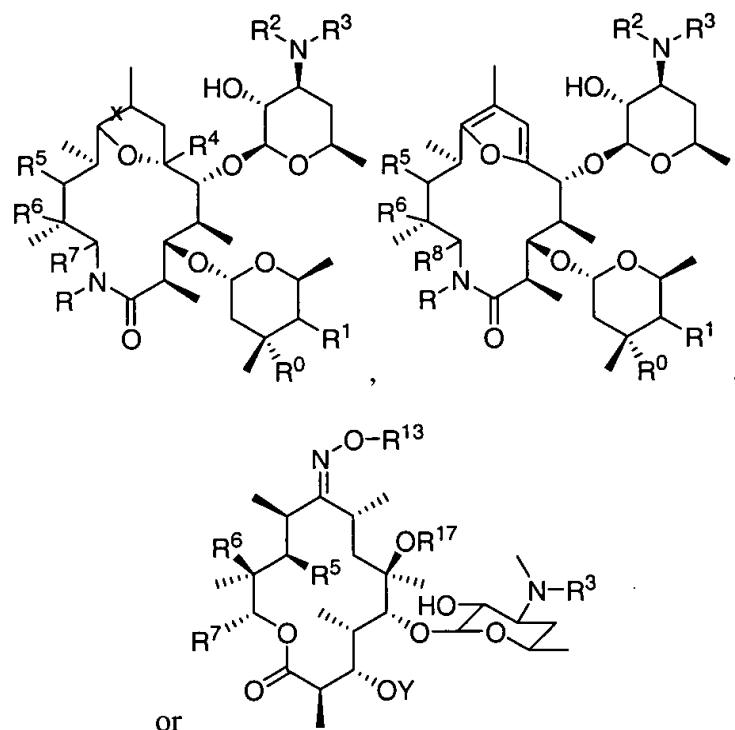
11. (Amended) The compound as in claim 7 of the formula



[wherein R¹ is hydroxyl, R³ is isopropyl and R⁷ is propyl].

18. (Amended) A method of treating a subject suffering from impaired GI motility comprising:

administering to said subject a therapeutically effective amount of a composition comprising a compound of claim 1 [the formula



wherein:

R is hydrogen, substituted C₁-C₁₀ alkyl, unsubstituted C₁-C₁₀ alkyl, substituted C₂-C₁₀ alkenyl, unsubstituted C₂-C₁₀ alkenyl, substituted C₂-C₁₀ alkynyl, unsubstituted C₂-C₁₀ alkynyl, substituted aryl, unsubstituted aryl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl;

R⁰ is hydroxyl or methoxy;

R¹ is selected from the group consisting of hydrogen, hydroxyl, halide, NH₂, OR⁹, $\text{O}=\text{C}-\text{R}^9$, $\text{O}=\text{C}-\text{N}(\text{R}^{10})\text{R}^{11}$, $\text{N}=\text{C}-\text{R}^9$, $\text{N}=\text{C}-\text{N}(\text{R}^{10})\text{R}^{11}$ where R⁹ is substituted C₁-C₁₀ alkyl, unsubstituted C₁-C₁₀ alkyl, substituted C₂-C₁₀ alkenyl, unsubstituted C₂-C₁₀ alkenyl, substituted C₂-C₁₀ alkynyl, unsubstituted C₂-C₁₀ alkynyl, substituted aryl, unsubstituted aryl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted

alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl, and R^{10} and R^{11} are each independently hydrogen, substituted C_1 - C_{10} alkyl, unsubstituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, unsubstituted C_2 - C_{10} alkynyl, substituted aryl, unsubstituted aryl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl;

R^2 and R^3 are each independently selected from the group consisting of hydrogen, substituted C_1 - C_{10} alkyl, unsubstituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, unsubstituted C_2 - C_{10} alkynyl, substituted aryl, unsubstituted aryl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl, or R^2 and R^3 together form a cycloalkyl or an aryl moiety;

R^4 is hydrogen or methyl;

R^5 is hydroxyl or oxo;

R^6 is hydrogen, hydroxyl, or OR^{12} where R^{12} is substituted C_1 - C_{10} alkyl, unsubstituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, or unsubstituted C_2 - C_{10} alkynyl;

R^7 is methyl, unsubstituted C_3 - C_{10} alkyl, substituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, unsubstituted C_2 - C_{10} alkynyl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl;

R^8 is unsubstituted C_1 - C_{10} alkyl, substituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, unsubstituted C_2 - C_{10} alkynyl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl;

R^{13} is hydrogen, unsubstituted C_1 - C_{10} alkyl, substituted C_1 - C_{10} alkyl, substituted C_2 - C_{10} alkenyl, unsubstituted C_2 - C_{10} alkenyl, substituted C_2 - C_{10} alkynyl, unsubstituted

C₂-C₁₀ alkynyl, subsubstituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, or unsubstituted alkynylaryl;

R¹⁷ is hydrogen or methyl;

x is a single or a double bond; and,

Y is hydrogen, substituted C₁-C₁₀ alkyl, unsubstituted C₁-C₁₀ alkyl, substituted C₂-C₁₀ alkenyl, unsubstituted C₂-C₁₀ alkenyl, substituted C₂-C₁₀ alkynyl, unsubstituted C₂-C₁₀ alkynyl, substituted aryl, unsubstituted aryl, substituted alkylaryl, unsubstituted alkylaryl, substituted alkenylaryl, unsubstituted alkenylaryl, substituted alkynylaryl, unsubstituted alkynylaryl, unsubstituted cladinose, or substituted cladinose].

19. (Amended) The method as in Claim 18 wherein the subject is a human suffering from gastroparesis, gastroesophageal reflux disease, anorexia, gall bladder stasis, postoperative paralytic ileus, scleroderma, intestinal pseudoobstruction, gastritis, emesis, [and] or chronic constipation (colonic inertia).

REMARKS

The Invention

The invention provides motilide compounds useful in the treatment of conditions characterized by impairment of gastric motility. The inventive compounds are semi-synthetic derivatives of erythromycin wherein the erythromycin 13-ethyl group is replaced with *n*-propyl. Surprisingly, the compounds provided by the present invention effective at stimulating gastric motility with without measurable induction of antibiotic activity. Thus, the compounds of the invention are useful for the treatment of such digestive disorders as gastroparesis and gastro-esophageal reflux disease.

Response to Restriction Requirement

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